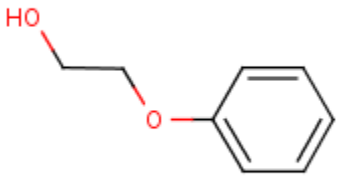
Phenoxyethanol

(CAS 122-99-6)

(Synonyms : Ethylene glycol monophenyl ether; Hydroxy-2-phenoxyethane; 2-Hydroxyethyl phenyl ether; 2-Phenoxyethanol; 2-Phenoxyethyl alcohol; Dowanol EP: EGMPE; Ethanol, 2-phenoxy- ; Ethylene glycol phenyl ether; Glycol monophenyl ether; Phenoxyethanol; Phenoxyethyl alcohol; Phenyl cellosolve; EGPE)



Phenoxyethanol Acute REL

No studies of short term exposure were located suitable for the derivation of an acute REL.

Phenoxyethanol 8-hour REL

Reference Exposure Level	**0.56 mg/m^3 (0.10 ppm)** [based on oral study]
Critical effects	Kidney enlargement
Hazard Index target	Kidney

1 Physical and Chemical Properties of Phenoxyethanol (EGPE)

Description	oily, colorless liquid
Molecular formula	$C_8H_{10}O_2$
Molecular weight	138.2 g/mol
Specific gravity	1.1094 @ 20°C/20°C
Boiling point	245° C
Melting point	14° C
Vapor pressure	0.03 mm Hg @ 25° C
Log Kow	1.16
Solubility	2.67×10^4 mg/l @ 20° C
Atmospheric half-life	3.9 hrs
Conversion factor	1 ppm = 5.5 mg/m^3

2 Production, Use, and Exposure

Phenoxyethanol (EGPE) is used as a solvent for cellulose acetate, dyes, inks, and resins, and in the organic synthesis of plasticizers, germicides, and pharmaceuticals. It is used as a solvent in paints and varnish removers. It is a topical antiseptic and insect repellent. It has been substituted for formaldehyde as a preservative of anatomical tissues, and is used as a fixative for perfumes and soaps. It has been used in some vaccines as an antibacterial agent to replace Thimerosal. EGPE is manufactured in a closed system by only one company in the U.S., so occupational exposure during production is minimal. Consumer use of EGPE as a solvent in paints, paint removers, oven cleaners, or in perfumes may result in dermal and inhalation exposures. However, due to its low vapor pressure, inhalation exposure is much lower than dermal exposure. Inhalation exposure is also limited by its relatively rapid degradation in the atmosphere. Systemic exposure may occur via ingestion and via vaccines containing EGPE as a preservative.

3 Pharmacokinetics and Metabolism

In mammalian cells, EGPE may be oxidatively metabolized by one or more alcohol dehydrogenases and aldehyde dehydrogenase to phenoxy acetic acid. Following dermal or oral exposure, the bulk of EGPE is eliminated in the urine as the parent compound and as phenoxy acetic acid (Howes, 1988 in (UNEP, 2004). In bacterial systems, EGPE is converted to phenol and acetaldehyde, with the latter subsequently converted to acetate.

4 Toxicity of EGPE

Acute exposure to EGPE may irritate the upper respiratory tract and, at higher concentrations, may result in central nervous system depression. Other symptoms reported include pronounced headache, abdominal pain, nausea, vomiting, and diarrhea. Transient polyuria, followed by oliguria progressing to anuria, and in some cases acute renal failure, is possible. Pathological lesions have been found in the brain, lungs, meninges, and heart. A maximum allowable workplace concentration (MAK) of 20 ppm was reported by NIOSH (2003).

No experimental studies were located that described the effects of EGPE inhalation in humans. However, the neurotoxic potential of EGPE was suggested in case reports by Morton et al.

(1990). In these reports, three women were occupationaly exposed dermally and possibly also by inhalation to EGPE used as an anesthetic for fish. All three experienced headaches and symptoms of intoxication, as well as diminished sensation and strength in their hands and fingers. Although a persistent neuropathy was not observed, after 1 – 2 years of exposure, the women showed a gradual onset of symptoms of cognitive impairment and an inability to work. In all three, persistent focal cognitive impairment was verified by neuropsychological testing.

Evidence for the potential neurotoxicity of EGPE was also seen in in vitro experiments in which rat-brain glutamate receptors were expressed in a Xenopus oocyte expression system (Musshoff et al., 1999). In this system, the effects of 17 glycol ethers on glutamate receptor-mediated ion currents were tested. Of these compounds, only EGPE caused a significant reduction in membrane currents induced by treatment with receptor agaonists, and then only with N-methyl-D-aspartate (NMDA), but not kainate, receptor agonists. The EGPE inhibitory effects on the NMDA subpopulation of glutamate receptors showed a dose response over the tested range of 10-500 µM EGPE. In general, disturbances of NMDA receptors may lead to decreased neuronal activity, and impairment of plasticity and learning processes. These effects are consistent with the symptoms of neurotoxicity reported above by Morton et al. (1999) for the three women occupationally exposed to EGPE.

In studies by Union Carbide (1949) and American Cyanamid (1966) (cited in UNEP, 2004), rats, and quail were exposed to room temperature atmospheres substantially saturated with EGPE for 7-8 hours. The animals showed no signs of toxicity, survived the 14-day observation period, and gained weight normally. Neither the actual EGPE concentrations nor the specific endpoints were described.

Following oral administration of EGPE, LD_{50}s of 2,937 and 4,013 mg/kg bodyweight were found for fasted male and female rats, respectively. By the dermal route, an LD_{50} of 14,300 mg/kg body weight was reported (UNEP, 2004).

In a repeated dosing study, rats were given EGPE at 80, 400, or 2,000 mg/kg body weight per day by oral gavage for 13 weeks. At 2,000 mg/kg, red blood cell toxicity was observed including decreased hemoglobin and red cell numbers, and kidney inflammation (Ben-Dyke et al, 1977 in UNEP, 2004). Mild tubular atrophy of the testes was observed in 1/15 controls and 3/15 test males at 2,000 mg/kg. Moderate tubular atrophy was observed in one test male at this dose. A lack of grooming was reported in the 2,000 and 400 mg/kg groups for the first 8 and 6 weeks, respectively. Kidney toxicity (inflammation) was seen at 400 and 2,000 mg/kg. The NOAEL in this study was 80 mg/kg/day, and used in the development of the RELs.

Hemolytic anemia has been associated with EGPE by both dermal and oral routes of exposure. Female New Zealand White rabbits were exposed by oral gavage to 100, 300, 600, or 1,000 mg/kg/day (three animals per dose) for 10 consecutive days (Breslin et al., 1991). On day 11, or prior to necropsy, blood was taken for hematological evaluation. All animals in the 1,000 mg/kg groups were dead or sacrificed moribund by the second day. All animals in the 600 mg/kg group were dead or sacrificed moribund by day six. In general, all rabbits exposed to EGPE had decreased red cell counts, packed cell volumes, and levels of hemoglobin, concomitant with increased nucleated and polychromatophilic red cells. Treatment-related microscopic changes

were seen in all treated animals. At the high doses, splenic changes included red pulp congestion and erythrophagocytosis. One rabbit in the 300 mg/kg groups had thrombi in venous sinuses and pulmonary blood vessels. Two animals in the 100 mg/kg group had splenic extramedullary hematopoiesis. Changes were also seen in kidney and stomach. The LOAEL for these effects was 100 mg/kg. The hemolytic anemia observed here is of uncertain toxicological consequence for humans, since human red blood cells exposed to glycol ethers are more resistant to hemolysis than are RBCs of sensitive species such as rats (Corley et al., 1994).

5 Derivation of Interim Acute (1-hour exposure) and 8-hour RELs for Phenoxyethanol (EGPE)

5.1 Derivation of Acute REL for PE.

No studies of short-term exposure to phenoxyethanol were located that were appropriate for the derivation of an acute REL. While an LD_{50} was reported, this value represents the upper limit for exposures that are compatible with survival without regard to protecting health. As such an LD_{50} is not the preferred basis for the derivation of an acute REL, which requires consideration of effects much less severe than lethality.

In the course of an 8-hour exposure, intermittent spikes in exposure levels are included in the time-weighted average addressed with the 8-hr REL. The values associated with 8-hr RELs are typically lower than allowed for acute 1-hr exposures, due to the longer exposure duration and possibility of recurring exposures. Therefore application of the 8-hr REL to exposure scenarios involving short-term peaks in concentration should be health protective in most cases.

5.2 Derivation of 8-Hour REL for EGPE.

Study	Ben-Dyke et al, 1977 in UNEP, 2004
Study population	Rats
Exposure method	Oral gavage
Exposure continuity	Once per day
Exposure duration	13 weeks
Critical effects	Kidney toxicity
LOAEL	400 mg/kg/d
NOAEL	80 mg/kg/d
LOAEL uncertainty factor	1 (NOAEL observed)
Subchronic uncertainty factor	√10
Interspecies uncertainty factor	
Toxicokinetic (UF_{A-k})	√10 (default for oral study)
Toxicodynamic (UF_{A-d})	√10
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	√10
Toxicodynamic (UF_{H-d})	10
Cumulative uncertainty factor	1000
Oral dose	0.08 mg/kg/d (80 mg/kg/d/1000)
Route to route extrapolation factor	3.5 kg/m^3/d (70 kg/20 m^3/d)
Chronic to 8-hr adjustment	2 (20 m^3/d/10 m^3/d)
8-hour Reference Exposure level	**0.56 mg/m^3** (0.08 mg/kg/d*3.5 kg/m^3/d*2)

The 8-hr REL is based on the observation of kidney enlargement in rats. A LOAEL of 400 mg/kg/d and a NOAEL of 80 mg/kg/d were observed in this subchronic study. In the absence of appropriate inhalation studies, this REL is based on the oral route of exposure. At 13 weeks in length, this study represents a subchronic exposure for which the default UF is √10. An interspecies uncertainty factor of 10 was applied, comprising √10 each for toxicokinetic and toxicodynamic variability between rabbits and humans. The intraspecies uncertainty factor of 30 comprises √10 for potential toxicokinetic variability, and 10 for toxicodynamic variability between adults and children. As observed in the Heindel et al. (1990) study described below, for reason that are not clear, immmature animals appear to be more susceptible to EGPE toxicity than are adults. The cumulative UF is 1000. This gave an oral dose of 0.08 mg/kg/d that should be without adverse health effects in humans. To convert this oral dose to an air concentration, it is assumed that the efficiency of absorption following an oral dose is the same as from the lungs during inhalation. The route-to-route conversion factor of 3.5 kg/m^3/d assumes a 70 kg adult (male) breathes 20 m^3 air/d. For the 8-hr REL, it is assumed that the air equivalent of the oral dose is taken in 8 versus 24 hours. The REL of 0.56 mg/m^3 is thus the oral dose (0.08 mg/kg/d) multiplied by the route to route conversion factor (3.5 kg/m^3/d), and by 2 (20 m^3/d/10 m^3/d) for the chronic (24 hr) to 8-hr conversion.

For comparison, NIOSH reports a MAK of 20 ppm (3.6 mg/m^3), and suggests that EGPE is irritating to the eyes, the skin, and the respiratory tract. This substance may cause effects on the central nervous system and peripheral nervous system, resulting in impaired functions. The

MAK value is higher than the 8-hr REL of 0.56 mg/m^3 described above as this REL is meant to protect the general public and therefore places more emphasis on the potential variability among individuals in their toxicokinetic and toxicodynamic responses to EGPE, and on the potentially greater toxicity to young versus adults animals as indicated in mice below.

6 Other toxicity

To assess the fetotoxic and teratogenic potential by the dermal route, EGPE was applied to the clipped skin of pregnant rabbits on gestational days 6-18 at 0, 300, 600, or 1000 mg/kg/day. Rabbits were treated with EGPE, and fetuses were examined for external, visceral, and skeletal alterations. Dermal application of 1000 mg/kg/day was maternally toxic as shown by intravascular hemolysis of red blood cells and death in some animals. Maternal toxicity was observed in rabbits treated with 600 mg EGPE/kg/day but at a lower incidence than that observed at 1000 mg/kg/day. Nine rabbits in the 1000 mg/kg/day dose group and five rabbits at 600 mg/kg/day died or were sacrificed *in extremis*. Rabbits in the two highest dose groups which survived until gestation day 28 showed no evidence of treatment-related effects. No signs of maternal toxicity were seen at 300 mg/kg/day. Examination of the fetuses indicated that EGPE was not embryotoxic, fetotoxic, or teratogenic at the dosages tested (Scortichini et al., 1987).

Reproductive toxicity has been reported for various glycol ethers. The effects of several glycol ethers, including EGPE, on testicular atrophy were compared in mice following oral gavage 5 days/week for 5 weeks. While the methyl- and ethyl ethers of ethylene glycol induced marked testicular atrophy, testis weights following EGPE exposure at 500 and 1,000 mg/kg were not significantly different from controls, although the ratio of testis to body weights tended to be lower at the higher dose (Nagano et al., 1984). The authors concluded that EGPE does not cause testicular atrophy. However, phenoxyethanol does appear to be a reproductive toxicant in female mice. In a continuous breeding reproduction study, Heindel et al. (1990) found that with EGPE at 0, 0.4, 2.0, and 4 g/kg body wt/day per os, there was no change in the ability to produce five litters during the continuous breeding period, but there was a small (10-15%) but significant decrease in the number of pups per litter and in pup weight in the high-dose group. A crossover mating trial suggested a female component of the reproductive toxicity of EGPE. While fertility was only minimally compromised, pronounced neonatal toxicity was observed in the form of persistent decreased weight gain, and increased lethality to the pups throughout lactation, weaning and puberty. It was not possible from this study to determine if the increased lethality was caused by EGPE-related lactation problems, or EGPE transferred in the milk. However, the observation that the offspring continued to die after weaning suggests that the immature rat is more sensitive to EGPE than the adult. By day 21 there were only 8 out of 40 litters in the mid- and high-dose groups which had at least one male and female per litter. Second generation reproductive performance of the mid-dose group (1.25%) was unaffected except for a small decrease in live pup weight. In summary the reproductive toxicity of EGPE was only evident in the female and occurred at doses that were maternally toxic. EGPE was also notably toxic to immature mice of both sexes at the 2 and 4 g/kg dose levels.

7 References

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